UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,161	04/12/2005	Irina Shcherbakova	50821/5	4723

7590 03/29/2006

Kevin B Laurence
Stoel Rives
One Utah Center
201 South Main Street Suite 1100
Salt Lake City, UT 84111

EXAMINER	
TRUONG, TAMTHOM NGO	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 03/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/531,161	SHCHERBAKOVA ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☒ Claim(s) *19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 are pending.

Specification

1. The disclosure is objected to because of the following informalities:

On page 51, the first line has chemical structure (of compound (93)) which does not have *fluoro* (or "F") group on the phenyl ring (of the *phenylethyl* group). However, the paragraph directly below the structure describes a process, which has the starting material of *2-(3-fluoro-phenyl)-ethylamine.* There is no step in which the *fluoro* group is displaced or cleaved. Thus, it appears that the described process is missing a step. Alternatively, it appears that compound (93) should have had the *fluoro* group on phenyl ring (of the *phenylethyl* group), or the starting material should have had an unsubstituted phenyl group.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a. In the definition of R^5, it is unclear if the listed substituents are only for the pyridyl and phenyl group, or if they are also intended for other groups such as: lower alkyl, furyl or thienyl as well.

b. Claim 1 recites R^7 as "*an aromatic group*" which has indefinite metes and bounds because it is unclear if heteroaryl group is also included in said limitation. The specification defines "aryl" group to have "*at least one ring having a conjugated or fused ring systems*" which suggests a polycyclic system. However, the preferred aryl group is an optionally substituted phenyl or pyridyl group, which is a monocycle. Thus, the definition of the aryl group is inconsistent with the preferred group.

d. Claim 14 recites the limitation of "*disease or disorder characterized by abnormal bone or mineral homeostasis*" which has indefinite metes and bounds because it encompasses a myriad number of unrelated diseases as listed in the specification in addition to those that have yet to be discovered. Therefore, it is not clear what disease is intended in such a treatment. The claim language reads on diseases not yet known to be caused by or affected by such an action, or in way not yet understood. The test for determining compliance with 35 U.S.C. 112, 2nd paragragph is whether applicants have clearly defined "their" invention not what may be discovered by future research as this type of claim language clearly requires.

e. Claim 17 recites the limitation of "*increasing serum parathyroid hormone*" which has indefinite metes and bounds. Like claim 14, such claim language reads on diseases not yet known to be caused by or affected by such an action, or in way not yet understood.

f. Claims 2-18 are rejected as being dependent on claim 1 and carrying over the indefinite limitations of R^5 and R^7.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Scope of Enablement:** Claims 14 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating osteoporosis, does not reasonably provide enablement for a method of treating other diseases that are allegedly related to *parathyroid hormone (PTH)*, or *abnormal bone or mineral homeostasis*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims:

Claim 14 recites: "A method of treating disease or disorder characterized by abnormal bone or mineral homeostasis..."

Claim 17 recites: "A method of increasing serum parathyroid hormone levels..."

The scope of the disease in both claims includes an extensive number of disorders as listed in the excerpt below:

> Diseases and disorders which might be treated or prevented, based upon the affected cells, include bone and mineral-related diseases or disorders; hypoparathyroidism; those of the central nervous system such as seizures, stroke, head trauma, spinal cord injury, hypoxia-induced nerve cell damage, such as occurs in cardiac arrest or neonatal distress, epilepsy, neurodegenerative diseases such as Alzheimer's disease, Huntington's disease and Parkinson's disease, dementia, muscle tension, depression, anxiety, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, schizophrenia, neuroleptic malignant syndrome, and Tourette's syndrome; diseases involving excess water reabsorption by the kidney, such as syndrome of inappropriate ADH secretion (SIADH), cirrhosis, congestive heart failure, and nephrosis; hypertension; preventing and/or decreasing renal toxicity from cationic antibiotics (e.g., aminoglycoside antibiotics); gut motility disorders such as diarrhea and spastic colon; GI ulcer diseases; GI diseases with excessive calcium absorption such as sarcoidosis; autoimmune diseases and organ transplant rejection; squamous cell carcinoma; and pancreatitis.
>
> In a preferred embodiment of the present invention, the present compounds are used to increase serum parathyroid hormone ("PTH") levels. Increasing serum PTH levels can be helpful in treating diseases such as hypoparathyroidism, osteosarcoma, periodontal disease, fracture, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy and osteoporosis.

The cited diseases affect different organs such as: heart, liver, GI, central nervous system (CNS), kidney, bone, pancreas,...etc. Furthermore, they do not share the same etiology, symptoms, manifestations, prognosis, etc. Thus, the scope of claims 14 and 17 is unduly broad.

The amount of direction or guidance presented:

The specification only describes *in-vitro* assay for detecting an increase of serum PTH, and inhibition of calcium receptor. It also generally discloses the preferred IC_{50} values of calcium receptor inhibition. However, it does not indicate which compounds have been tested. Thus, even for *in-vitro* activity, one cannot ascertain whether any of the claimed compounds would have an effect on PTH or calcium receptor. Given the relationship of PTH and osteoporosis, it would be reasonable to expect the claimed compound to treat osteoporosis. As for other diseases encompassed by the scope of "*abnormal bone or mineral homeostasis*", the specification has not provided sufficient enablement in term of practical data for the skilled clinician to use the claimed compound in commensurate with the scope of claims 14 and 17.

The state of the prior art:

As evident by many references cited in the art rejection below, the majority of quinazolinone compounds is used as intermediates, or in the treatment of cardiovascular disorders. None of the cited references relate quinazolinone to the serum of PTH, or inhibition of calcium receptor. Thus, the state of the prior art does not support the scope of the treatment recited in claims 14 and 17.

The relative skill of those in the art:

Even with the advanced training, the skilled clinician would have to engage in extensive research to select an effective compound from the large Markush group of the claimed quinazolinone formula. Not only one has to determine an IC_{50} value, but also *in-vivo* activity to establish an LD_{50}, therapeutic index and pharmacokinetic profile for each compound. Given a large Markush group of the claimed quinazolinone formula, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary:

The pharmaceutical art has been known for its unpredictability due to various conflicting path ways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the specification only describes *in-vitro* bioassay without an indication of any compounds tested. However, said description alone does not adequately guide the skilled clinician in the treatment of diseases affecting various organs and systems with different underlying factors.

Also, no compound has ever been found to treat diseases of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. Note, substantiation of utility and its scope is required when utility is "speculative", or "sufficiently unusual". See ***Ex parte Jovanovics***, 211 USPQ 907, 909; ***In re Langer*** 183 USPQ 288. Also, see ***Hoffman v. Klaus*** 9 USPQ 2d 1657, and ***Ex parte Powers*** 220 USPQ 925 regarding type of testing needed to support *in vivo* uses.

Thus, with such a limited teaching, the skilled clinician would have to engage in undue experimentation to use the claimed compounds in the methods recited in claims 14 and 17.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 9 and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by **Carpino et. al.** (US 6,337,332 B1 or US'332). On column 28 of US'332, Table 2 lists compound 2c which reads on the instantly claimed quinazolinone formula with the following substituents:

i. R^1-R^3, each represents hydrogen;

ii. X^1 is carbon; R^4 is alkoxy;

iii. R^5 is a styryl group substituted with halogen;

iv. R^6 is hydrogen.

The disclosed compound is used to treat obesity and circulatory disorders, and thus, the pharmaceutical composition of claim 13 is also anticipated.

5. Claims 1-3, 5-9 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by the following references:

a. **Amschler et. al.** (US 3,984,555): Several quinazolinone intermediates on columns 8 and 9 (e.g., *2-(chloro-, bromo- or iodo-methyl)-4-(3H)-quinazolone*) read on compounds of the instant claims 1, 2 and 5-9 when the instantly claimed quinazolinone formula has the following substituents:

i. X^1 is C;

ii. R^1-R^4, each is hydrogen; or

iii. R^1 is hydrogen, and R^3-R^4, each can be an alkyl or alkoxy group;

iv. R^5 is lower alkyl substituted with a halogen;

v. R^6 is hydrogen.

b. **Wright, Jr. et. al.** (US 4,710,502): On column 4, the 6th compound in Table 1 reads on compounds of the instant claims 1-3, 5-9, and the pharmaceutical composition of the instant claim 13 when the instantly claimed quinazolinone formula has the following substituents:

i. X^1 is C;

ii. R^1, R^3 and R^4, each is hydrogen; or

iii. R^2 is halogen;

iv. R^5 is hydrogen;

v. R^6 is $-(CH_2)_n$-X^2-R^7;

vi. X^2 is an alkyl group; n = 2;

vii. R^7 is an aromatic group (i.e., *imidazolyl* group).

c. **Mederski et. al.** (WO 01/23365 A1): On page 71, several compounds (e.g., compounds on lines 20, 24 and 29) read on compounds of the instant claims 1-3, 5-9, and the pharmaceutical composition of the instant claim 13 when the instantly claimed quinazolinone formula has the following substituents:

i. X^1 is C;

ii. R^1 and R^4, each is hydrogen; or

iii. R^2 is halogen or an alkyl group;

iv. R^3 is halogen or an alkoxy group;

v. R^5 is a phenyl group substituted with a halogen;

vi. R^6 is $-(CH_2)_n-X^2-R^7$;

vii. X^2 is a direct bond; n = 1;

viii. R^7 is an aromatic group (i.e., *phenyl* group) substituted with an alkyl group which in turn is substituted with an amino group. Note, since the limitation of "lower alkyl" is opened for substitution.

d. **Sadhu et. al.** (WO 01/81346 A2): On page 166, the intermediate 6a (e.g., compounds on lines 20, 24 and 29) reads on compounds of the instant claims 1-3, 6-9 when the instantly claimed quinazolinone formula has the following substituents:

i. X^1 is C;

ii. R^1 is halogen;

iii. R^2 - R^4, each is hydrogen; or

iv. R^5 is an alkyl group substituted with hydroxy;

v. R^6 is $-(CH_2)_n-X^2-R^7$;

vi. X^2 is a direct bond; n = 0;

vii. R^7 is an aromatic group (i.e., *phenyl* group) substituted with an alkyl group which in turn is substituted with an amino group. Note, since the limitation of "lower alkyl" is opened for substitution.

Claim Objections

6. Claim 19 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 19 recites species with the combination of *hydroxyl-phenyl* at the 2nd position, and *phenyl(or pyridyl)-ethyl* at the 3rd position of the quinazolinone ring, which is not taught or fully suggested by the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Tamthom N. Truong
Examiner
Art Unit 1624

***

3-19-06

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600